Clinical Aspects of Aconitum Preparations*

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Abstract

Aconite species have played an important role in human history. *Aconitum* species have been used worldwide as poisons as well as remedies. Their potential in targeting several ailments such as pain, rheumatism, and lethargy has been recognized by Western, Chinese, and Indian health care practitioners. Aconite use in herbal preparations has declined, especially in Europe and the United States, in the first half of the twentieth century due to several reported toxicity cases. The situation has changed with the application of new technologies for the accurate analysis of its toxic components and the development of efficient detoxification protocols. Some Asian countries started small clinical trials to evaluate the potency and safety of different marketed aconite preparations. The current review summarizes therapeutic uses of aconite preparations in China, Taiwan, India, and Japan. It also highlights clinical trial results with special emphasis on their limitations. Modern drugs and pharmacopoeial preparations derived from aconite are also discussed.

Introduction

Aconitum, also known as monkshood, wolf's bane, or devil's helmet, has been widely used in folk medicine in China, India, and certain parts of Europe [1–4]. The genus *Aconitum* (Ranunculaceae) comprises 300 species distributed all over the world [5]. The most common species are *Aconitum carmichaelii* Deb. and *Aconitum kusnezoffii* Rchb. in China, *Aconitum japonicum* Thunb. in Japan, *Aconitum napellus* L. in Europe, *Aconitum ferox* Wall. ex Ser. in India, and *Aconitum noveboracense* A. Gray ex Coville in the United States [5].

Several classes of secondary metabolites, especially alkaloids, have been isolated from different *Aconitum* sp. [6]. The type of the isolated major alkaloids may vary depending on the species such as aconitine, hypaconitine, and mesaconitine from *A. carmichaelii*, aconitine from *A. napellus*, hypaconitine from *A. septentrionale* Koelle, mesaconitine from *A. kusnezoffii*, bikhaconitine from *A. ferox*, talatisamine from *A. kongboense* Lauener, atisine from *A. anthora* L., and *A. heterophyllum* Wall. ex Royle, and lycaconitine from *A. vulparia* Rchb. [6]. Several isoquinoline alkaloids and phenethylamine derivatives have also been isolated, such as higenamine from *A. japonicum*, magnoflorine from *A. vulparia* and *A. napellus*, coryneine from *A. carmichaelii*, and N-methyl adrenaline from *A. nasutum* Fisch. ex Rchb. [6]. Lipo-alkaloids including lipoaconitines, lipomesaconitines, lipodeoxyaconitines, and lipohypaconitines were also isolated [7,8].

The efficacy of *Aconitum* sp. in resolving critical clinical conditions has been proven by doctors practicing traditional Chinese medicine (TCM) and Ayurvedic medicine for centuries. However, the long history of *Aconitum* sp. misuse in homicide cases has shaken the faith in the potential safe application of this herb in therapy [9,10]. The recent developments in analytical techniques which can identify and determine the concentrations of toxic compounds in herbal products with impressive accuracy and reliability have rekindled the interest in *Aconitum* preparations [1,5,6,11,12].

A plethora of studies have focused on developing accurate, feasible, and fast analytical techniques to determine the alkaloidal content in each acon-

* Dedicated to Professor Dr. Dr. h.c. mult. Adolf Nahrstedt on the occasion of his 75th birthday.

# These authors contributed equally to this work.

Table 1 Famous formulas with Fuzi.

Formula	Ingredients	Fuzi dosage
Sini Tang	*Aconitum carmichaelii* (**Raw** Fuzi), *Zingiber officinale* (Ganjiang), and *Glycyrrhiza uralensis* (roasted Gancao, licorice)	1 piece (15–30 g)
Bai Tong Tang	*Allium fitulosum* L. (white stem of shallot), *Zingiber officinale* (Ganjiang), and *Aconitum carmichaelii* (**Raw** Fuzi)	1 piece (15–20 g)
Fuzi Lizhong Tang	*Aconitum carmichaelii* (**Processed** Fuzi), *Panax ginseng* (ginseng), *Zingiber officinale* (Ganjiang), *Atractylodes macrocephala* Koidz. (Bai Zhu), *Glycyrrhiza uralensis* (roasted Gancao, licorice)	1 piece (15–20 g)
Ma Huang Fuzi Hsi Hsin Tang	*Ephedra sinica* (Ma Huang), *Aconitum carmichaelii* (**Processed** Fuzi), and *Asarum sieboldii* (His Hsin)	1 piece (15–20 g)
Jen Wu Tang	*Poria cocos* F. A. Wolf. (Fu Ling), *Paeonia lactiflora* Pallas. (Shaoyao, Chinese peony), *Zingiber officinale* (fresh ginger), *Atractylodes macrocephala* Koidz. (Bai Zhu), and *Aconitum carmichaelii* (**Processed** Fuzi)	1 piece (15–20 g)
Fuzi Tang	*Aconitum carmichaelii* (**Processed** Fuzi), *Poria cocos* F. A. Wolf. (Fu Ling), *Panax ginseng* (ginseng), *Atractylodes macrocephala* Koidz. (Bai Zhu), and *Paeonia lactiflora* Pallas. (Shaoyao, Chinese peony)	2 pieces (30–40 g)
Ma Huang Fuzi Gancao Tang	*Ephedra sinica* (Ma Huang), *Aconitum carmichaelii* (**Processed** Fuzi), *Glycyrrhiza uralensis* (roasted Gancao, licorice)	1 piece (15–20 g)
Gui Zhi plus Fuzi Tang	Ramulus Cinnamomi, *Cinnamomum cassia* (Gui Zhi), *Paeonia lactiflora* Pallas. (Shaoyao, Chinese peony), *Glycyrrhiza uralensis* (roasted Gancao, licorice), *Zingiber officinale* (fresh ginger), *Ziziphus jujuba* Mill. (jujube), *Aconitum carmichaelii* (**Processed** Fuzi)	1 piece (15–20 g)

ite preparation using trivial analytical equipment available in almost all analytical laboratories [13–18]. Also, the biological effects of different *Aconitum* sp. *in vitro* and *in vivo* have been studied in depth, revealing the molecular targets of each major component [19–21]. Recently, studies reporting the clinical applications of different *Aconitum* preparations have revealed promising results in terms of safety and efficacy [22, 23]. However, an overview summarizing clinical studies on *Aconitum* sp., which can help in further developments, is still lacking. This review aims to provide a comprehensive summary of the clinical applications of *Aconitum* preparations. To fully understand the potential of this herb in therapy, a short introduction on the clinical use of *Aconitum* sp. throughout history based on reliable historical records is presented.

Traditional Chinese Medicine

Aconitum was first introduced in Shennong Ben Cao Jing, which is the earliest Chinese herbs book and might be written around the era of Qin to Western Han Dynasties (221–200 BC) [24, 25]. Aconitum preparations, including Fuzi (aconiti radix lateralis praeparata), Wutou (chuan wu, aconiti radix praeparata), and Caowu (*A. kusnezoffii*), have been recommended for cold limbs, painful knees, walking difficulties, chronic wounds, poor circulation, spasms, and different tumors [3].

The applications of *Aconitum* were advocated in Shang Han Lun, which was written by Zhang Zhongjing, one of the most respected TCM physicians in history. He lived in the Eastern Han Dynasty around 150–209 AD [26]. He introduced some formulas (**Table 1**) [26] targeting critical health problems using Fuzi as the main therapeutic agent. In addition to the indications summarized in Shang Han Lun, Fuzi was mainly used to treat patients with general weakness, fatigue, drowsiness, cold extremities, abdominal pain, bone pain, and weak pulse. It was believed that Fuzi was highly effective in improving body circulation [5, 27–29].

Aconitum toxicity remained a major concern to TCM practitioners, and many prominent physicians in the Ming to Qing Dynasties were afraid to use Fuzi in herbal formulas [5]. This cautious trend continued until the renaissance TCM theory in the Han to Tang Dynasties. The physicians living in this period found out that following therapeutic theories introduced by Zhang Zhongjing resulted in impressive results. Spreading this knowledge to the rest of the world started in the nineteenth century with the surge of migration waves from China to Western countries [30]. Many TCM practitioners found that *Aconitum* played an important role in the history of Western civilization as a lethal herb and as a medication. Through combining knowledge accumulated over centuries from Eastern and Western civilizations, TCM practitioners started to advocate the use of *Aconitum* against several ailments. Hai-Ha Ni (1954–2012) in the USA, Bu-Tao Chang (1942–2012) in Taiwan, Chin-An Zheng (1824–1911) in China, and other prominent TCM physicians introduced different therapeutic regimens containing Fuzi. *Aconitum* was prescribed for its cardiotonic, antiarrhythmic, analgesic, anti-epileptiform, anticancer and antimicrobial activities [3]. In order to maximize the clinical effects, some followers of Chin-An Zheng recommended the use of raw or processed Fuzi in a dose as high as 60–120 g, which was 4–8 times the dosage recommended by previous practitioners. However, the pros and cons of high doses of Fuzi were not investigated.

Practitioners have differentiated in their recommendations between raw and processed Fuzi. In general, raw Fuzi was administrated in more critical conditions, while the processed preparation was used to increase circulation and energy [5]. Recent scientific studies showed that the toxicity of raw Fuzi is reduced by processing due to the hydrolysis of the ester group of the diester-diterpenoid alkaloids (aconitine, mesaconitine, and hypaconitine) (**Fig. 1**) [4]. Initially, the acetyl group is hydrolyzed and in the second step, the benzoyl group is hydrolyzed (**Fig. 2**) [17]. This process results in an increase in the concentrations of monoester-diterpenoid alkaloids (benzoylaconine, benzoylmesaconine, and benzoylhypaconine) in the processed Fuzi [18]. Also, the concentration of lipo-alkaloids, which are esters of alkaloids with fatty acids in the C-8 position, significantly increased after processing (**Fig. 3**) [8]. However, there is no detailed clinical study showing the differences in pharmacological activity and toxicity between raw and processed Fuzi. Therefore, it is important to conduct such studies on a reasonable scale to demonstrate the potential and limitations of raw and processed Fuzi. One of the important steps to tackle this problem is the ongoing randomized control trial to evaluate the efficacy of Sini Tang, which uses raw Fuzi, in patients with septic shock [31]. It is hoped that such trials will provide health care authorities with essential in-

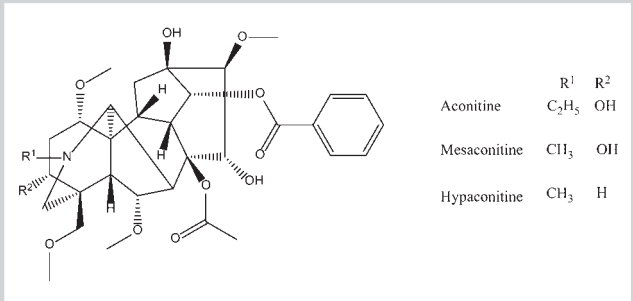

Fig. 1 The main toxic *Aconitum* diterpene alkaloids.

formation to establish the necessary measures and regulations of *Aconitum* use.

Current Herbal Formulas in China

In China, many scientists, physicians, and pharmaceutical companies work together to create new *Aconitum*-based formulas. Many different hospitals create their own formulas and they also try to formulate Fuzi into pills, capsules, and injections instead of traditional decoctions [28, 29]. The clinical results of different *Aconitum* formulas reported in English are summarized below.

Qili-qiangxin capsules

The qili-qiangxin capsule was developed and approved in 2004 by the Chinese Food and Drug Administration for the treatment of heart failure [32]. Its development was based on the theory of TCM. The formula contains 11 distinct herbs, in which astragali radix and aconiti lateralis radix preparata (Fuzi) are the principal pharmacologically active components.

One thousand capsules were prepared from ginseng radix et rhizome (225 g), astragali radix (450 g), aconiti lateralis radix preparata (112.5 g), semen descurainiae lepidii (150 g), *Salvia miltiorrhiza* Bunge (Lamiaceae) radix et rhizome (225 g), alismatis rhizoma (225 g), ramulus cinnamomi (90 g), polygonati odorati rhizoma (75 g), periplocae cortex (150 g), carthami flos (90 g), and citri reticulatae pericarpium (75 g) [33]. Each capsule was 0.3 g, and patients were advised to take four capsules each time three times a day.

The clinical efficacy of qili-qiangxin capsules in treating heart failure was proved after the publication of a double-blind, multicenter, placebo-controlled, prospective, randomized clinical trial in 435 patients with chronic heart failure in 2013 [34]. Patients included in the trial were diagnosed with heart failure and were found to belong to class II–IV according to the New York Heart Association (NYHA) functional classification. They suffered from a left ventricular ejection fraction (LVEF) ≤ 40% and a serum NT-proBNP (N-terminal pro–B-type natriuretic peptide) level ≥ 450 pg/mL. The possible causes of heart failure were cardiomyopathy (56.82%), ischemic heart disease (32.59%), or hypertension (19.75%). In addition, 15.48% of the patients had a medical history of atrial fibrillation and 16.7% had diabetes mellitus.

The results showed that the qili-qiangxin capsule group demonstrated improved symptoms compared to the placebo group after 12 weeks of follow-up. Patients in the qili-qiangxin capsule group (47.95%) showed a reduction in plasma NT-proBNP compared with 31.98% of the patients in the placebo group. Treatment with qili-qiangxin capsules also resulted in superior performance in comparison to the placebo group with respect to NYHA functional classification, LVEF, 6-min walking distance, and quality of life. The detailed mechanism of the qili-qiangxin capsule in treating heart failure is not well established yet. An animal study showed that the qili-qiangxin capsule could downregulate the ratio of tumor necrosis factor-α/interleukin-10 and improve cardiac function in mice with myocardial infarction [35]. It also inhibited myocardial inflammation and the death of cardiomyocytes. On the other hand, it promoted cardiomyocyte proliferation, leading to improved cardiac remodeling and cardiac function [36]. Another study showed that qili-qiangxin improved both systolic and diastolic cardiac functions, and it downregulated the cardiac chymase signaling pathway and chymase-mediated angiotensin II production in hypertensive rats [37]. The other cardioprotective effects of qili-qiangxin were related to the regulation of the glycolipid substrate metabolism by activating AMPK (AMP-activated protein kinase)/PGC-1α (peroxisome proliferators-acti-

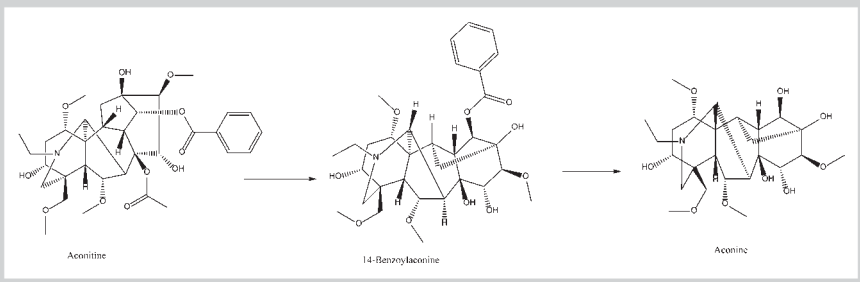

Fig. 2 Decomposition of aconitine during the processing of aconite.

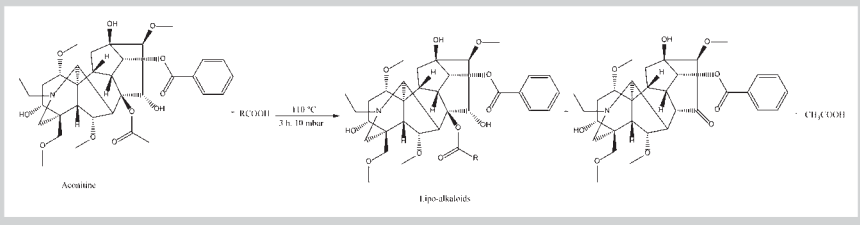

Fig. 3 General scheme for transesterification reaction.

vated receptor-γ coactivator-1α) axis. Also, it was suggested that qili-qiangxin reduced the accumulation of free fatty acids and lactic acid protecting cardiac myocytes and mitochondrial function [38].

Regarding the electrophysiological aspects of qili-qiangxin, it was found that the capsule blocks $I_{Ca\text{-}L}$ (L-type Ca^{2+} channel) and reduces Ca^{2+} overload. These effects can improve the heart rate similar to the effect of antiarrhythmic agents and improve the overall condition of the heart [39]. Qili-qiangxin was also found to decrease the sodium current (I_{Na}), transient outward K^+ current (I_{to}), and activate the delayed rectifier outward K^+ current (I_{Ks}) on cardiac ventricular myocytes [40]. These results suggested the potential application of qili-qiangxin capsules as a treatment for heart failure and arrhythmia.

Shenfu injection

Shenfu injection (SFI) is one of the modern formulations of Chinese medicine, which is prepared from red ginseng [steamed roots of *Panax ginseng* C.A.Mey. (Araliaceae)] and aconite (processed lateral roots of *A. carmichaelii*) by using countercurrent extraction and macroporous resin adsorption chromatography [41]. A total of 44 components were identified by the high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (HPLC-QTOF MS) method [41]. An LC-MS method with selected ion monitoring was used to quantify 24 major alkaloids and ginsenosides. The total content of ginsenosides was found to be 676–742 µg/mL, while the alkaloids were present in trace amounts (3–7 µg/mL). In the SFI sample, ginsenosides Rb1 Rg1, and Re were the predominant components, followed by Rc, Rf, and Rb2.

Its clinical application was evaluated against a myriad of ailments including heart failure, septic shock, intradialytic hypotension, post-resuscitation care, cancer, and neuroprotection. A systemic review and meta-analysis study were conducted to evaluate the efficacy of SFI for the treatment of heart failure [42]. The mortality rate in patients with myocardial infarction-induced heart failure was significantly decreased in the shenfu injection (SFI) group. However, the mortality rates in patients with heart failure that was not caused by myocardial infarction was not affected by SFI. On the other hand, the cardiac function in the SFI group was improved according to NYHA classification, not only in myocardial infarction-induced heart failure but also in non-myocardial infarction-induced heart failure. The results of echocardiography also showed that SFI combined with routine treatment such as beta-blockers, ACEI, antihypertensive agents, and diuretics improved left ventricular ejection fraction (LEVF), cardiac output, stroke volume, and the cardiac index (CI) in heart failure patients. SFI also improved the E/A ratio [the ratio of the early (E) to late (A) ventricular filling velocities]. In a healthy heart, the E velocity is greater than the A velocity. In certain pathologies and with aging, the left ventricular wall can become stiff, increasing the back pressure as it fills, which slows the E filling velocity, thus lowering the E/A ratio [43]. The reversal of the E/A ratio (A velocity becomes greater than E velocity) is often accepted as a clinical marker of diastolic dysfunction, suggesting that diastolic function was improved in the SFI group. In the evaluation of biological parameters, SFI significantly reduced NT-proBNP levels and increased the distance of 6-min walking. However, there was no significant difference in blood pressure between the SFI and routine treatment groups.

In the treatment of intradialytic hypotension (IDH), SFI also showed a beneficial effect in hemodialytic patients. Eight randomized, controlled clinical trials were performed with 348 participants during 7974 hemodialysis sessions to evaluate the effect of SFI [44]. The results showed that SFI significantly increased systolic blood pressure but not diastolic blood pressure. The SFI group also showed an improved clinical effective rate compared with the control group. SFI reduced the incidence of hypotension when used to prevent or to treat an episode of intradialytic hypotension (IDH). The albumin level was increased but the C-reactive protein (CRP) level was decreased in patients treated with SFI. No significant side effects were reported. For the management of septic shock, one Chinese systemic review, which included 499 patients in six randomized, controlled trials, concluded that SFI could increase systolic and diastolic blood pressure [45]. It also improved shock symptoms and reduced the heart rate.

Other studies tried to evaluate the effect of SFI in improving the quality of life as well as in treating cancer-related fatigue and anemia [46,47]. However, the presented results were insignificant. In general, well-organized, controlled clinical trials should be conducted to evaluate the previously reported Shenfu animal studies. These reports indicated that Shenfu acted as a coronary dilator [48] as well as a neuroprotective agent after cardiac arrest [49], post-resuscitation care [50], acute pancreatitis [51], and hypoxic-ischemic brain injury [52]. In addition to qili-qiangxin capsules and SFI, many hospitals are trying to develop other kinds of Fuzi-related formulations with special emphasis on its cardiotonic effect. It is recommended that clinical trials should be conducted in different countries and not only restricted to China to fully exploit the benefits of *Aconitum* preparations.

Aconitum in Ayurvedic Medicine

Ayurvedic medicine is the Indian traditional medicinal system. Ayurvedic medicine includes the use of herbal, mineral, or metal products as well as surgical techniques and massages. The origin of Ayurvedic medicine is unclear. Some records in Atharvaveda might be written around 1500–1000 BC [53–56]. These records contain 114 hymns and incantations described as magical cures for different diseases, forming the origin of Ayurvedic medicine [53].

Different *Aconitum* sp. were used by practitioners of Ayurvedic medicine in the preparation of herbal formulas targeting several disorders. However, scientific literature lacks reports on clinical trials evaluating Ayurvedic herbal formulas containing *Aconitum*. Information on the clinical efficacy of *Aconitum* preparations comes from the traditional use of this herb over centuries [57, 58]. There are 11 *Aconitum* sp. used in Ayurvedic medicine. They are used as anti-inflammatory, antiemetic, antirheumatic, and antidiarrheal agents. The details are summarized in **Table 2** [57].

Current Applications of Fuzi in Taiwan

In Taiwan, Fuzi is strictly regulated due to its toxicity. According to the Taiwan Herbal Pharmacopeia, the total concentration of diester-diterpenoid alkaloids (aconitine, mesaconitine, and hypaconitine) should not be above 0.020% in crude Fuzi materials. On the other hand, the total concentration of monoester-diterpenoid alkaloids (benzoylaconine, benzoylmesaconine, and benzoylhypaconine), the less toxic alkaloids, should be over 0.010% [59]. The suggested dosage of crude Fuzi is 3–15 g.

Table 2 Common *Aconitum* species in Ayurvedic medicine.

Species	Ayurvedic name	Action	Main alkaloid components
Aconitum atrox	Vatsanaabha	Poison	1.2% Total alkaloids, psuedoaconitine (0.4%)
Aconitum chasmanthum	Visha, Shringika-Visha	Sedative, antirheumatic, analgesic, antitussive, antidiarrhea	Aconitine, mesaconitine, hypaconitine, 3-acetylaconitine, lappaconitine, benzoconine
Aconitum deinorrhizum	Vatsanaabha	Rheumatism, rheumatic fever and acute headache	0.9% Total alkaloids, 0.4% psuedoaconitine
Aconitum falconeri	Vatsanaabha	Sedative; carminative; anti-inflammatory for the nervous system and digestive system	Bishatisine, bishaconitine, falconitine, and mithaconitine
Aconitum ferox	Vatsanaabha, Visha, Amrita, Vajraanga, Garala	Narcotic, sedative, antileprotic, anti-inflammatory	Diterpenoid alkaloids
Aconitum heterophyllum	Ativishaa, Arunaa, Vishaa, Shuklakandaa, Bhanguraa	Antiperiodic, fever, antispasmodic (abdominal pain and stomach), anti-inflammatory, astringent (cough, diarrhea, dyspepsia)	0.79% Total alkaloids, atisin 0.4%
Aconitum laciniatum	Vatsanaabha	Poison	
Aconitum luridum	Vatdanaabha	As potent as *Acoitum ferox*	
Aconitum palmatum	Prativishaa, Shyaamkandaa, Patis	Antiemetic, anti-diarrhea, antirheumatic, antiperiodic	Diterpenoid alkaloids, benzamide, vakognavine, palmatisine, vakatisine, vakatisinine, and vakatidine
Aconitum spicatum	Vatsanaabha	Antipyretic, analgesic	1.75% Alkaloids, mainly pseudoaconitine and bikhaconitine
Aconitum violaceum	Vatsanaabha	Nervine tonic	1% Indaconitine

There are not only crude preparations of Fuzi in Taiwan but also commercial products of Fuzi extraction concentrated powder/granules. However, some of the famous Fuzi formulations do not have commercial concentrated TCM powder. After our evaluation, the commercial powder/granule products only include processed Fuzi, Ma Huang Fuzi Hsi Hsin Tang, Fuzi Lizhong Tang, Sini Tang, Jen Wu Tang, and Guifu Dihuang Wan (Ba Wei Di Huang Wan).

We examined commercial concentrated Fuzi powder in two GMP TCM factories. The concentrations of alkaloids were quantified by HPLC-UV [60]. A commercial Fuzi powder (1 g) was extracted from 2.5 g crude drug in factory A. The concentrations of the total diester-diterpenoid alkaloids and monoester-diterpenoid alkaloids were ca. 12 and 16 ppm, respectively (10 ppm = 0.001%). On the other hand, a commercial Fuzi powder (1 g) was extracted from 3.35 g crude drug in factory B. The concentrations of the total diester-diterpenoid alkaloids and monoester-diterpenoid alkaloids were ca. 9 and 10 ppm, respectively. Compared with the requirement of crude Fuzi, the concentrations of toxic alkaloids were quite low. Therefore, the usage of commercial Fuzi powder/granule products is considered to be safer than crude Fuzi. Due to the difficulty of controlling the crude drug quality, it might be a good alternative to control the concentrated extract/granule powder products. It can help to set the standard criteria in many kinds of Fuzi formulas and it may be beneficial to investigate their efficacy in advanced clinical practice.

Aconite Preparations in Kampo Medicine

Kampo medicine is a Japanese medical system derived from TCM, which might have passed to Japan during the Tang Dynasty around 700–800 AD [61–63]. Kampo medicine focuses on herbs, acupuncture, and moxibustion. Many classical TCM books such as Huangdi Neijing, Shennong Ben Cao Jing, and Shanghan Lun set the standard of the treatment theory. Since then, Japanese doctors have improved the theory borrowed from TCM according to their clinical experiences and observations. Many famous Japanese doctors such as Tashiro Sanki (1456–1537), Nagoya Geni (1628–1696), and Yoshimasu Todo (1702–1773) contributed significantly to its progress. Ishizaka Sotetsu (1770–1841) and Honma Soken (1804–1872) even tried to incorporate Western medicine theory into Kampo medicine [64].

Influenced by Western medicine, Japanese physicians tried to apply Kampo formulas to Western medical diseases. In order to set the standard of its clinical practice, physicians used fixed combinations of herbs in standardized proportions, which may be derived from TCM formulas or Japanese physicians. They fit the indications of these formulas one by one to Western diseases based on clinical evidence. There are more than 148 Kampo formulas approved as prescription drugs, which accounts for 1.34% of the total number of prescriptions in Japan [65]. Physicians in Japan not only prescribe Western medicine but also Kampo medical herbs. According to a nationwide study in 2000, almost 72% of physicians have prescribed Kampo medical herbs [66]. Such an attitude has a great influence on the development of Kampo medicine.

Aconite is used in Kampo medicine because of the deep influence by Shanghang Lun. Due to its toxicity, scientists analyzed the alkaloid content, nuclear DNA region, and internal transcribed spacer (ITS) from 107 *Aconitum* plants in Japan [67] and set the standard analytical method in the Japanese pharmacopeia [68]. The pharmacokinetics and toxicology of *Aconitum* preparations or powders were also studied [69, 70]. It was revealed that aconite tuber can regulate peripheral vascular function by increasing the plasma levels of nitrite and nitrate, which was in agreement with the theory of Kampo medicine [71].

The analgesic effect of *Aconitum* was also investigated. A case series study showed that 12 postherpetic neuralgia patients showed improvement in a visual analogue pain scale under the treatment combination of Keishikajutsubuto (TJ-18) 7.5 g/day and Bushi-matsu (TJ-3022) 1.0–5.0 g/day [72]. The results of animal studies supported the analgesic effect of *Aconitum* formulas such as Tsumura-shuuji-bushi-matsu [73] and kako-bushi-matsu [74].

Table 3 Formulas with aconite in Kampo medicine.

Formula name	Ingredients	Indications/Dosage
Gosha-jinki-gan. (Tsumura, Jpn.)	7.5 g of TSUMURA Goshajinkigan extract granules (TJ-107) contain 4.5 g of a dried extract of the following mixed crude drugs: Rehmannia root 5.0 g, achyranthes root 3.0 g, cornus fruit 3.0 g, dioscorea rhizome 3.0 g, plantago seed 3.0 g, alisma rhizome 3.0 g, poria sclerotium 3.0 g, moutan bark 3.0 g, cinnamon bark 1.0 g, powdered processed aconite tuber 1.0 g.	Patients with decreased urine volume or polyuria sometimes having dry mouth who are easily fatigued and easily feel cold in the extremities: Leg pain, low back pain, numbness, blurred vision in old patients, pruritus, dysuria, frequent urination, and edema. Usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals.
Hachimi-jio-gan. (Tsumura, Jpn.)	7.5 g of TSUMURA Hachimijiogan extract granules (TJ-7) contain 4.0 g of a dried extract of the following mixed crude drugs: Rehmannia root 6.0 g, cornus fruit 3.0 g, dioscorea rhizome 3.0 g, alisma rhizome 3.0 g, poria sclerotium 3.0 g, moutan bark 2.5 g, cinnamon bark 1.0 g, powdered processed aconite root 0.5 g.	Patients with severe fatigue or malaise, decreased urinary output or increased urinary frequency, dry mouth, and alternate cold and hot feeling in the extremities: Nephritis, diabetes mellitus, impotence, sciatica, low back pain, beriberi, cystorrhea, prostatic hypertrophy, and hypertension. Usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals.
Keishikajutsubuto. (Tsumura, Jpn.)	7.5 g of TSUMURA Keishikajutsubuto extract granules contain 3.75 g of a dried extract of the following mixed crude drugs: Cinnamon bark 4.0 g, peony root 4.0 g, atractylodes lancea rhizome 4.0 g, jujube 4.0 g, glycyrrhiza 2.0 g, ginger 1.0 g, aconite root 0.5 g.	Neuralgia, arthralgia. Usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals.
Shuchibushi N. (Tsumura, Jpn.)	*Aconitum carmichaeli* root.	

The famous aconite Kampo medicine preparations and their indications are listed in ▶ **Table 3** [62, 63, 65, 75]. It shows that *Aconitum* is applied in many different clinical situations. The efficacy of some formulations has been proven by small clinical studies. For example, Gosha-jinki-gan was shown to have a benefit in the treatment of lymphedema [75, 76].

Some Kampo formulations are directly derived from TCM. For example, Shinbuto is similar to Jen Wu Tang, Shigyakuto resembles Si Ni Tang, and Maobushisaishinto is derived from Ma Huang Fuzi Hsi Hsin Tang. Hachimi-jio-gan, with the same ingredients as Ba Wei Di Huang Wan in TCM, showed a beneficial effect in improving MMSE (Mini-Mental State Examination). It also improved the activities of daily living (ADLs) score in the Barthel Index in severe dementia patients after an eight-week treatment course in a randomized, double-blind, placebo-controlled trial [77].

Aconitum in Homeopathy

Homeopathy is a system of alternative medicine created by the German physician Samuel Hahnemann (1755–1843) [78]. Hahnemann advocated the principle that effective drugs produce symptoms in healthy individuals similar to those of the diseases that they treat, like cures like. He used medical herbs to treat diseases. The first usage of *A. napellus* in homeopathy was recorded in Materia Medica Pura, which was written by Samuel Hahnemann in 1810. *A. napellus* was prescribed as an antipyretic and anti-inflammatory agent. It was also recommended to overcome fear, neuralgia, and urinary problems [79]. However, the effectiveness of *A. napellus* in homeopathy is still controversial. In a randomized, double-blind, controlled crossover study, *A. napellus* C30 (dilution of 10^{60} times) yielded statistically significant results between the classified reactions compared with the placebo in healthy volunteers [80].

One prospective observational study showed similar efficacy of using different homeopathic remedies (*A. napellus, Apis mellifica*, Belladonna, Capsicum, Chamomilla, Kalium bichromicum, Lachesis, Lycopodium, Mercurius solubilis, Okoubaka, Pulsatilla, Silicea) to treat pediatric otitis media compared with nasal drops, antibiotics, secretolytic agents, and antipyretics in relieving symptoms [81]. Due to the lack of clinical studies, the efficacy and indication of *A. napellus* in homeopathy cannot be assured. More rigorous clinical evaluations are needed in the future.

Drugs Containing *Aconitum* sp. or *Aconitum* Alkaloids

Aconite use in drugs remains a controversial issue because of its extreme toxicity and the unpredictability of patients' response. Despite this drawback, the potent effect of this herb has encouraged pharmaceutical companies in some European and Asian countries to include aconite in minute quantities in different herbal preparations. Unfortunately, scientific literature lacks a concise summary of these drugs, which may assist physicians, practitioners, and health care authorities in their decision to introduce aconite into the mainstream therapeutic regimens. We have checked several pharmacopoeias (Japanese [68], European [82], British [83], and International Pharmacopeia by WHO [84]) as well as Martindale: The Complete Drug Reference [85] and Remington: The Science and Practice of Pharmacy [86] with the aim of providing a list for drugs containing aconite (▶ **Table 4**).

Besides the clinical studies on traditional aconite preparations, there is a growing trend to analyze some *Aconitum* alkaloids as potential therapeutic agents. Lappaconitine (or more precisely lappaconitine hydrobromide known as Allapinin) was the first orally active drug to be registered as a medicine in 1987 in the former Soviet Union after successful preclinical and clinical studies [87–89]. Interestingly, the starting point of the research on cardioactive alkaloids was based on the assumption that certain structurally close analogs of aconitine-type arrhythmogenic alkaloids may possess an antiarrhythmic effect. An extensive investigation of the antiarrhythmic effect of 82 diterpene alkaloids and their derivatives on animal models led to the identification of a series of pharmacologically promising substances, possessing similar or better activity (ED_{50}) than traditional antiarrhythmic agents (e.g., procainamide and ethmosine) with a higher thera-

Table 4 List of drugs containing aconite.

Name of the drug/country	Ingredients	Indications
Aconit Schmerzo/Austria	Aconite	Homeopathic preparation
Aconitum Med Complex/Germany	Aconite	Homeopathic preparation
Aconitum Nicotiana comp/Germany	Aconite	Homeopathic preparation
Aconitum-Homaccord/Austria	Aconite	Homeopathic preparation
Agrimel/Brazil	Aconite, rorippa nasturtium aquaticum, tolu, ipecacuanha	Cough
Anti-Gripe/Portugal	Aconite, belladonna, codeine, caffeine, andparacetamol	Cold symptoms, fever, pain
Andromaco/Chile	Codeine, bromoform, aconite, belladonna, grindelia, drosera, sodium benzoate, cherry-laurel water	Cough
Broncofenil/Brazil	guaifenesin, lobelia, and aconite	Cough
Broncorinol toux seche/France	pholcodine, sodium benzoate, aconite, hyoscyamus, lobelia, senega, and eucalyptus	Cough
Calm/Australia	Passion flower, aconitum nap, belladonna, chamomilla	Insomnia, irritability or restlessness in children
Calmarum/Portugal	Sulfogaiacol, ephedrine hydrochloride, ethylmorphine (dionina), sodium benzoate, aconite, thyme, and senega	Cough
Cold & Flu Respatona Dry Cough Relief/Australia	Anise oil, marshmallow, white bryony, Iceland moss, echinacea, chamomile, thyme, urtica, aconite, ammonia, coccus cacti, corallium rubrum, drosera rotundifolia, ipecacuanha, kali bich., kreosotum, spongia tosta, sticta pulmonaria	Cough
Colimax/Belgium	Ephedrine hydrochloride, sodium benzoate, aconite, belladonna, thyme, wild thyme, maidenhair fern	Cough
Cough Relief/Australia	Anise oil, althaea, bryonia, Iceland moss, echinacea, chamomile, thyme, urtica, *Aconitum nap*., coccus cacti, corallium rub., drosera, ipecacuanha, kali bich., kreosotum, spongia tosta, sticta pulm	Cough
Encialina/Spain	Aconite, arnica, ipecacuanha, chamomile, rhatany, iodine	Mouth inflammation, pyorrhea
Eucalyptine Pholcodine Le Brun/Belgium	Sulfogaiacol, sodium camsilate, sodium phenolsulfonate, pholcodine, belladonna, aconite, cineole	Respiratory disorders
Expectomel/Brazil	Rorippa nasturtium aquaticum, aconite, ipecacuanha, senega, tolu balsam, honey, guaco	Respiratory tract congestion
Hachimi-jio-gan/Japan	Rehmannia root, cornus fruit, dioscorea rhizome, alisma rhizome, poria sclerotium, moutan bark, cinnamon bark, aconite tuber	Traditional Kampo medicine
Keishikajutsubuto/Japan	Cinnamon bark, peony root, atractylodes lancea rhizome, jujube, liquorice, ginger, aconite root	Traditional Kampo medicine
Lactocol/Italy	Guaiacol, lactic acid, calcium phosphate, calcium lactate, codeine hydrochloride, aconite	Cough
Melagriao/Brazil	*Nasturtium officinale*, aconite, mikania glomerata, ipecacuanha, senega, tolu balsam, honey	Respiratory tract congestion
Padma/Switzerland	Aconite, aegle sepiar, amomi fruit, aquilegia, calendula, camphor, cardamom, clove, costus root, hedychii rhizome, lettuce, Iceland moss, liquorice, meliae tausend, myrobalani, ribwort plantain, knotgrass, golden potentilla, sandalwood bark, sidae cordifoliae, valerian, calcium sulfate	Circulatory disorders
Pectal/Brazil	Sodium dibunate, aconite, cineole, grindelia, mikania glomerata, senega	Cough
Pleumolysin/Czech Republic	Codeine phosphate, thyme, gypsophila saponin, aconite, bitter-orange peel	Coughs, respiratory tract inflammation
Vifor/Switzerland	Ethylmorphine hydrochloride, ulfogaiacol, sodium benzoate, belladonna, hyssopus officinalis, tolu balsam	Coughs, respiratory tract disorders
Xarope de Caraguata/Brazil	*Annona muricata*, bromoform, sodium benzoate, aconite, belladonna, tolu balsam, grindelia	Cough

peutic index (LD_{50}/ED_{50}) [90]. Such potent activity encouraged researchers to subject lappaconitine to further studies. Large-scale protocols have been developed for the extraction and purification of this alkaloid from the roots of *Aconitum leucostomum* Vorosch. and *A. septentrionale* [91].

Clinical studies started in the 1980 s, focusing on the effect of lappaconitine on the hemodynamics and myocardial contractility of patients with heart rhythm disorders [92]. The drug proved to be effective as class 1 C antiarrhythmic drugs. It was more effective than ethmozine and ethacizine in preventing ventricular and supraventricular extrasystoles. This effect was demonstrated in a clinical trial with patients suffering from arrhythmias of different etiology [93]. In paroxysmal ventricular tachycardia, lappaconitine hydrobromide had a similar efficacy to ethacizine and bonnecor [94], even in the case of long-term treatment [95]. In paroxysmal supraventricular arrhythmia, it exerted similar preventive antiarrhythmic efficacy to the class 1 antiarrhythmic drugs tachmalcor and propafenone [96]. According to a review on clinical trials, lappaconitine hydrobromide is especially effective in the prevention of paroxysmal atrial fibrillations [97]. A recently published study reported its efficacy in preventing ventricular premature beats [98]. Allapinin, similar to class IC antiarrhythmic drugs, causes a prolonged blockade of cardiomyocytes Na^+ channels; however, contrary to other drugs such as lidocaine, it acts reversibly only on open channels. Moreover, recent studies revealed that lappaconitine hydrobromide decreased mRNA levels

for the gene coding of certain K^+- and Na^+-channels and membrane transporter genes [99].

Furthermore, acehytisine (former name Guanfu base A), a diterpene alkaloid isolated from *Aconitum koreanum* R. Raymond, has been approved for the treatment of paroxysmal supraventricular tachycardia in 2005 in China [100]. In a study, patients with sustained supraventricular tachycardia using intravenous acehytisine hydrochloride showed comparable results to the group under propafenone [101]. In a further study, the intravenous administered alkaloid had similar efficacy to propafenone in controlling the premature ventricular contraction [102]. This compound blocks the fast Na^+-channel, the delayed rectifier potassium current, and the L-type calcium current; however, it does not induce Q_T interval prolongation [100]. These two alkaloids are currently used in the market due to their favorable benefit-risk ratio compared to other, conventional antiarrhythmic drugs.

Toxicity of Aconite Preparations

The toxicity of *Aconitum* is notorious, as mentioned in all ancient records. Shakespeare highlighted the potency of this herb in his novel Romeo and Juliet, in which he stated that Romeo committed suicide using this poison [103]. Also, in Macbeth, the witches' brew calling for "tooth of wolf" refers to monkshood. Certain species are known also as wolfsbane because arrows dipped in the poison kill wolves. The emperor Trajan (98–117 AD) banned the growing of this plant in all Roman domestic gardens [104]. One of the most remarkable pieces, which described the role played by this plant in ancient Roman society, was summarized by the writer Ovid [104]. He referred to aconite as the "step-mother's poison". In the first Potions class in Hogwarts, Prof. Severus Snape informed Harry Potter about the toxicity of wolfsbane, which is the main ingredient of Wolfsbane Potion [105].

In recent years, many cases of *Aconitum* poisoning were published worldwide. Cases were concentrated in the Far East, with few cases in India or Europe. Until 2006, there were over 600 reported cases of *Aconitum* poisoning in China [106]. In Taiwan, 17 cases were reported from 1990 to 1999 [107]. In Hong Kong, the incidence of aconite poisoning was estimated to be 0.60 per 100 000 populations from 1989 to 1993. But the annual incidence of herb-induced aconitine poisoning in the New Territories East in Hong Kong significantly decreased to 0.17 per 100 000 populations after the publicity measures from 1996 to 1998 [108].

In general, *Aconitum* poisoning results from the direct oral intake of *Aconitum* decoctions or pills. Toxicity through dermal penetration is rare and only 14 cases of poisoning have been reported following the topical application of aconite preparations until 2011 [109]. In the two fatal cases, the epidermis and dermis at the sites of application were already damaged as a result of hot water scalding or herpes zoster infection. Both of the victims applied self-prepared aconite tincture, and one of them used raw "caowu (*A. kusnezoffii*)" 8 g and raw "chuanwu" 8 g in the application, which is even considered an overdose under normal circumstances. It was also suggested that the absence of an intact epidermis (*stratum corneum*) due to injury or diseases might significantly increase the systemic absorption of *Aconitum* alkaloids. To improve the safety of topical *Aconitum* preparations, alkaloid content is maintained as low as possible (0.119 mg per plaster) by manufacturers, but their use should be under medical supervision [110].

A study reported four "hidden" *Aconitum* poisoning cases, which did not include aconite in their prescriptions. *Aconitum* involvement was suspected due to the similarity of poisoning symptoms. Moreover, yunaconitine, which is not one of the common toxins (aconitine, hypaconitine, and mesaconitine), was also speculated to be involved in aconite toxicity [111]. Although it is uncommon, this may be just the tip of an iceberg with some cases going unrecognized.

The clinical presentation of *Aconitum* poisoning varies depending on the situation. From the experience of TCM doctors, the first symptom of *Aconitum* poisoning might be numbness of the tongue and lips. Other common symptoms are as follows: paresthesia and numbness over the face and limbs, nausea, dizziness, vomiting, abdominal pain, cold sweating, palpitations, bradycardia, tachycardia, hyperventilation, chest tightness, and hypotension. The mean latent period is 43.6 min [107], but it may differ depending on the dosage. Electrocardiography in these patients may show ventricular tachycardia, ventricular fibrillation, premature ventricular contractions, multifocal ventricular ectopics, sinus tachycardia, and bradycardia [107–109, 112]. There is no specific dose-response relationship in these studies. Furthermore, it may elevate troponin-I and creatine kinase (CK), which mimics acute myocardial infarction [113].

The treatment of *Aconitum* poisoning depends on supportive care, some physicians tried $MgSO_4$, lidocaine, atropine, current shock, and a temporary pacemaker to correct patients' heart rhythm [107, 112]. The toxicokinetic information is not well established in aconite poisoning. One study showed that the aconitine half-life is 3.7–17.8 h, its AUC is 2.4–5.1 ng × h/mL, and its mean residence time is 10.8–23.6 h. Mesaconitine half-life is 2.8–5.8 h, its AUC is 5.4–13.0 ng × h/mL, and its mean residence time is 9.7–11.9 h. Jesaconitine half-life is 5.8–15.4 h, its AUC is 6.9–33.5 ng × h/mL, and its mean residence time is 11.5–22.6 h. The range is wide because of the influence of liver and kidney function in herbal detoxification [112]. After appropriate treatment, most patients can recover without a specific sequela within eight days [107].

According to these studies, it is generally understood that the usage of *Aconitum* sp. should be under clinical supervision to prevent toxicity. More clinical trials should be conducted to reveal the optimum dosage, processing method, and formulations.

Detoxification Protocols

In ancient times, TCM practitioners tested several methods to reduce the toxicity of raw Fuzi. Some healers increased the decoction time, which led to a significant reduction in toxicity. Others mixed the herb with radix glycyrrhizae, *P. ginseng*, or *Zingiber officinale* Roscoe (Zingiberaceae) to decrease the toxicity of Fuzi and enhance its efficacy [114]. For example, Sini Tang is formed of radix glycyrrhizae (Gancao) and *Z. officinale* (Ganjiang) in combination with raw Fuzi. The effect of this preparation was attributed to the interaction between glycyrrhizin, liquiritin, and Fuzi alkaloids [115]. Furthermore, additional processing methods were developed over the years, including soaking in water, stir-frying, boiling, roasting, and steaming [116].

Some excipients were added during processing, including salts, green beans, licorice, and ginger, to reduce toxicity and improve efficacy. Yanfuzi, Heishunpian, Baifupian, Danfupian, and Paofupian are common processed products in Asian markets [106] (**Table 5**). All of the mentioned processing methods helped to

Table 5 Common Fuzi detoxification protocols in China.

Product name	Processing methods
Yanfuzi	Soaked with salts ($MgCl_2$ or NaCl) and dried in the sun. The surface of Fuzi is usually covered with salts.
Heishunpian	Soaked with salts and boiled in water, resulting in the formation of a transparent mass. This mass is sliced and brown sugar with oil is added giving the slices a brown color. Slices are then steamed, roasted, and dried.
Baifupian	Soaked with salts and boiled in water, leading to the formation of a transparent product. This product is sliced, steamed, and smoked with sulfur, rendering the slices white in color. Slices are then roasted and dried.
Danfupian	Yanfuzi is cleaned from salt by soaking in water. The product is sliced, boiled with licorice and black beans, and finally dried in the sun.
Paofupian	Yanfuzi salt is removed by soaking in water. The preparation is then sliced, soaked with ginger juice, roasted, and fried.

reduce Fuzi toxicity by decomposing DDAs to the less toxic monoester-diterpenoid alkaloids (MDAs) [117]. After processing, the content of the highly toxic DDAs is generally reduced 40- to 70-fold compared to raw Fuzi.

Indian healers used different methods for the detoxification of aconite preparations known as Shodhana. It is based on treating the herb with cow dung, cow urine, or cow milk and subjecting the treated material to sunlight for a certain period of time using special containers [118]. Kampo practitioners added other nontoxic herbs to aconite roots such as cinnamon and atractylodes (Keishibukuryogan) as well as Ma-huang and asarum (Maobushisaishinto) [119]. Asian decedents and Asian communities in other countries followed TCM practitioners detoxifying protocols with minor modifications [120].

The regulations of these toxic products differ among countries. It can only be imported or exported under strict regulations. The total amount of aconitine, hypaconitine, and mesaconitine should be less than 0.020% in aconitine products in China and Taiwan [106]. In Japan and Europe, extra restrictions are applied and the concentration of toxic alkaloids (DDAs) is further reduced [121]. The concentrations of the nontoxic alkaloids should not exceed 3%, such as aconitic, malic, quinic, chlorogenic, and caffeic acid. In the USA and Canada, there are no specific regulations on *Aconitum* preparations, and reported toxic cases were mainly due to misidentification and misuse of the herb [122]. Different analytical techniques were developed to analyze and quantify the concentrations of aconitine alkaloids, including HPLC, LC-MS, LC-MS/MS, and electrophoresis, with impressive accuracy and speed [3, 17, 18].

Conclusion

Aconite has been and will remain a mysterious herb. It is like Janus in Greek mythology with two faces, one supports healing and the other leads to death. Its long history of use did not eliminate suspicion and confusion about its true nature. TCM, Kampo, and Ayurvedic practitioners have studied this herb in depth and introduced a plethora of protocols to reduce its toxicity. Serious clinical trials have just started in China in the last decades aiming to reveal aconite's true therapeutic potential. These trials suggested that qili-qiangxin capsules and SFI are efficient in treating heart diseases. Homeopathy and Ayurveda therapeutic systems have used aconite for centuries, but without any reported clinical trials. Practitioners of Kampo medicine have performed small trials, which suggested potent aconite analgesic activity. Despite such attempts, the global official aconite usage is still in its infancy. It is recommended to conduct more clinical trials on different populations using available *Aconitum* sp. The results of these trials will assist health care authorities to regulate and control aconite preparations for the safety and benefits of patients.

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Conflict of Interest

The authors declare no conflict of interest.

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